CURRENT THERAPEUTIC RESEARCH

VOLUME 67, NUMBER 1, JANUARY/FEBRUARY 2006

Effects of Atorvastatin 10 mg/d on Insulin Resistance: A 12-Week, Open-Label Study in Hyperlipidemic Patients

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ABSTRACT

Background: In addition to their cholesterol-lowering effects, hydroxymethylglutaryl coenzyme A reductase inhibitors ("statins") might have pleiotropic, nonlipid effects. Insulin resistance syndrome is known to increase the risk for cardiovascular disease. However, the effects of statins on insulin resistance are a subject of controversy.

Objective: We aimed to investigate the effects of atorvastatin on insulin resistance in hyperlipidemic patients.

Methods: This 12-week, prospective, nonrandomized, open-label study was conducted at the outpatient cardiology clinic, Ege University Medical School, Bornova-Izmir, Turkey. Hyperlipidemic patients aged ≥18 years with insulin resistance and no other components of the metabolic syndrome were included in the study. Atorvastatin 10 mg QD (after the evening meal) was administered by mouth (tablet) over a 12-week period. At baseline and after 12 weeks of treatment, insulin sensitivity was assessed using homeostasis model assessment (HOMA) index methodology. Serum lipid parameters and fasting levels of plasma glucose and insulin (FPG and FPI, respectively) were measured at the same 2 time points. The tolerability of atorvastatin was assessed using laboratory analysis and physical examination, including vital sign measurements.

Results: Fifteen white patients (9 women, 6 men; mean [SD] age, 52 [8] years) participated in the study. No significant changes in HOMA index were found (mean [SD], 3.1 [1.5] vs 3.2 [1.9]). The lipid profile was improved significantly at 12 weeks compared with baseline (mean [SD] low-density lipoprotein cholesterol, 173.2 [21.3] vs 110.8 [43.6] mg/dL; total cholesterol, 270.9 [21.5] vs 201.2 [46.7] mg/dL; and triglycerides, 269.5 [46.3] vs 205.5 [49.3] mg/dL; all, $P < 0.001$). No significant change in mean (SD) plasma high-density lipoprotein cholesterol level (45.5 [6.6] vs 43.7 [8.1] mg/dL) was found. In addition, no significant changes in FPG (85.3 [12.7] vs 84.8 [10.4] mg/dL), or FPI (13.5 [9.7] vs 13.9 [10.1] μU/mL) were found. None of the patients required withdrawal of medication due to an adverse event.

Accepted for publication December 7, 2005.

doi:10.1016/j.curtheres.2006.02.002
0011-393X/06/$19.00

Conclusion: In this pilot study in hyperlipidemic patients with insulin resistance, 12 weeks of treatment with atorvastatin 10 mg QD was effective in controlling hyperlipidemia but did not reduce the severity of insulin resistance. (*Curr Ther Res Clin Exp.* 2006;67:44–54) Copyright © 2006 Excerpta Medica, Inc.

Key words: atorvastatin, insulin resistance, hyperlipidemia, statin therapy.

INTRODUCTION

The metabolic syndrome, also known as *Reaven syndrome* or *insulin resistance syndrome*, increases the risk for cardiovascular disease (CVD).[1–3] The metabolic syndrome is the consequence of genetic predisposition and lifestyle factors (eg, obesity-inducing dietary habits, physical inactivity).[1] Characteristics of the metabolic syndrome are abdominal obesity (body mass index [BMI], ≥30 kg/m^2, given that BMI and waist circumference >102 cm [men], >88 cm [women] are strongly correlated), dyslipidemia (triglyceride [TG] level, ≥150 mg/dL; high-density lipoprotein cholesterol [HDL-C] level, <40 mg/dL in men and <50 mg/dL in women), hypertension (systolic blood pressure [SBP], ≥130 mm Hg; diastolic blood pressure [DBP], ≥85 mm Hg; or receiving antihypertensive treatment), elevated fasting plasma glucose (FPG) (≥110 mg/dL), impaired glucose tolerance or diabetes mellitus (DM), microalbuminuria (30–300 mg/dL), and prothrombotic and proinflammatory states.[4] Insulin resistance plays a key role in the pathogenesis of the metabolic syndrome.[1] A number of studies have investigated the correlation between insulin resistance and the components of the metabolic syndrome, especially with DM, abdominal obesity, and/or hypertension.[5] In particular, the relationship between DM and the atherosclerotic process has been examined in detail.[6–8] However, based on a MEDLINE search (key terms: *hyperlipidemia* and *insulin resistance*), data are limited regarding the presence of insulin resistance in hyperlipidemic patients who have no other CVD risk factors that are components of the metabolic syndrome.

In addition to their cholesterol-lowering effects, hydroxymethylglutaryl co-enzyme A reductase inhibitors ("statins") modify endothelial function, inflammatory response, and thrombus formation on atheromatous plaques.[9–12] Insulin resistance increases the mitogenic activation of growth factors on the atheromatous plaques, and it might result in platelet aggregation, thrombus formation, and endothelial dysfunction.[13] Statins have nonlipid pleiotropic effects.[10,11] The results of several studies of the effects of statin treatment on hyperlipidemic patients with type 2 DM have been contradictory.[14–16] One study[14] found that statin treatment improved insulin action. But the other findings[15,16] were a lack of any effect on insulin resistance or a worsening of insulin action. The pleiotropic effects of statins, especially corrective effects on endothelial dysfunction, might decrease the severity of insulin resistance.[12]

Our study aimed to investigate the effects of atorvastatin on insulin resistance in hyperlipidemic patients.

PATIENTS AND METHODS

Study Population and Design

This 12-week, prospective, nonrandomized, open-label study was conducted at the outpatient cardiology clinic at Ege University Medical School, Bornova-İzmir, Turkey. This was a convenience sample. Male and female hyperlipidemic patients aged ≥18 years with insulin resistance (homeostasis model assessment [HOMA] index,[17] >2.7[18]), plasma total cholesterol (TC) level >240 mg/dL, a TG level between 200 and 400 mg/dL, despite receiving the American Heart Association Step I diet[19] for at least 12 weeks before the study, and stable body weight for 8 weeks before the study were enrolled.

Patients were excluded from the study if they were obese (BMI, >30 kg/m^2), hypertensive (SBP/DBP, ≥130/≥85 mm Hg, or receiving antihypertensive medication), had impaired glucose tolerance (FPG level, ≥110 mg/dL or plasma glucose >140 mg/dL on 2-hour 75-g oral glucose tolerance test), hepatic insufficiency (serum aspartate aminotransferase or alanine aminotransferase activity, ≥2-fold the upper limit of normal [× ULN]), renal insufficiency (serum creatinine level, ≥2.0 mg/dL), serum creatine kinase activity ≥3 × ULN, secondary pathologies leading to hyperlipidemia (eg, renal or thyroid dysfunction), and/or intensive alcohol consumption habits. Patients were also excluded if they were being treated with medications affecting insulin, glucose, or lipid metabolism. Patients with psychiatric abnormalities and women who were pregnant, could become pregnant, or were breastfeeding were also excluded.

The study protocol was approved by the Turkish Society of Cardiology project and ethics board. All details of the study were explained to the patients, and all patients provided their written consent before they entered the study. Patients were not allowed to receive any additional medications during the study. Patients were requested to continue following the American Heart Association Step I diet[19] throughout the study.

Study Drug Administration

Patients received atorvastatin 10 mg QD (after the evening meal) by mouth (tablet) for 12 weeks.

Efficacy and Tolerability Assessments

The primary end point of the present study was the change from baseline (week 0) to study end (week 12) in the HOMA index. The secondary end points were changes from baseline to study end in serum levels of TC, HDL-C, low-density lipoprotein cholesterol (LDL-C), and TG; FPG; and fasting plasma insulin (FPI).

Fasting blood samples were collected to determine lipid parameters before study drug administration on day 1 and at the end of the 12-week treatment period. Routine biochemistry and tolerability assessments were conducted at baseline and weeks 4 and 12.

Serum levels of TC, HDL-C, and TG were assessed enzymatically using an autoanalyzer (Dax 48, Bayer Diagnostics, Toshiba, Japan). LDL-C level was cal-

culated using the Friedewald formula.[20] Serum levels of apolipoprotein (apo) A1 and apo B were assayed using an autoanalyzer (model 704, Hitachi, Tokyo, Japan) with turbidimetry (Boehringer Mannheim GmbH, Mannheim, Germany). FPI level was measured using an enzyme immunoassay method (Coat-A-Count Insulin, Diagnostic Products Corporation, Los Angeles, California). The presence of insulin resistance was assessed using the HOMA index[17] at baseline and 12 weeks. A HOMA index >2.7 was considered to be insulin resistance.[18] BMI was measured and waist/hip ratio was calculated in each patient before and after treatment. Sitting blood pressure and pulse rate were measured at baseline and 12 weeks. Blood pressure was measured in the same arm each time by the same person, using a standard cuff sphygmomanometer. The median of 3 measurements was used.

The tolerability of atorvastatin was assessed using laboratory analysis and physical examination, including vital sign measurements, and documentation of the type, frequency, severity, duration, and relationship to treatment of any adverse events. Patients were directly asked about adverse events.

Statistical Analysis

Because of the small number of study patients, the Wilcoxon rank sum test was applied to assess the differences in values between baseline and after 12 weeks of atorvastatin treatment. $P < 0.05$ was considered significant. Statistical analyses were performed using SPSS version 10.0 (SPSS Inc., Chicago, Illinois). All values are expressed as mean (SD).

RESULTS

The study population comprised 15 white patients (9 women, 6 men; mean [SD] age, 52 [8] years). None of the patents had significant disease.

Efficacy

No significant changes between baseline and 12 weeks of atorvastatin treatment were found in BMI or waist/hip ratio (26.8 [2.7] vs 26.5 [2.3] kg/m^2 and 0.90 [0.04] vs 0.90 [0.07], respectively). Atorvastatin significantly lowered fasting serum levels of LDL-C (173.2 [21.3] vs 110.8 [43.6] mg/dL), TC (270.9 [21.5] vs 201.2 [46.7] mg/dL), and TG (269.5 [46.3] vs 205.5 [49.3] mg/dL) (all, $P < 0.001$). No statistically significant difference was found in HDL-C level (45.5 [6.6] vs 43.7 [8.1] mg/dL) after treatment. Apo B level decreased significantly (147.6 [16.5] vs 102.3 [19.7] mg/dL; $P < 0.001$), whereas apo A1 level did not change significantly (131.7 [38.2] vs 130.4 [15.7] mg/dL). No significant changes were found in FPG (85.3 [12.7] vs 84.8 [10.4] mg/dL) or FPI (13.5 [9.7] vs 13.9 [10.1] μU/mL). No statistically significant difference in the HOMA index was observed at the end of treatment (3.1 [1.5] vs 3.2 [1.9]) (**Table I**).

Table I. Clinical characteristics before (baseline) and after 12 weeks of treatment with atorvastatin 10 mg/d in patients with hyperlipidemia and insulin resistance (N = 15). Values are mean (SD).

Characteristic	Baseline	12 Weeks	*P*
BMI, kg/m^2	26.8 (2.7)	26.5 (2.3)	0.683
WHR	0.90 (0.04)	0.90 (0.07)	1.000
LDL-C, mg/dL	173.2 (21.3)	110.8 (43.6)	<0.001
HDL-C, mg/dL	45.5 (6.6)	43.7 (8.1)	0.495
TC, mg/dL	270.9 (21.5)	201.2 (46.7)	<0.001
TG, mg/dL	269.5 (46.3)	205.5 (49.3)	<0.001
Apo A1, mg/dL	131.7 (38.2)	130.4 (15.7)	0.901
Apo B, mg/dL	147.6 (16.5)	102.3 (19.7)	<0.001
FPG, mg/dL	85.3 (12.7)	84.8 (10.4)	0.897
FPI, μU/mL	13.5 (9.7)	13.9 (10.1)	0.903
HOMA index*	3.1 (1.5)	3.2 (1.9)	0.898

BMI = body mass index; WHR = waist/hip ratio; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides; apo = apolipoprotein; FPG = fasting plasma glucose; FPI = fasting plasma insulin; HOMA = homeostasis model assessment.[16]
*HOMA index >2.7 = insulin resistance.[17]

Tolerability

No significant differences in SBP (124.1 [12.7] vs 128.3 [12.4] mm Hg), DBP (78.7 [9.4] vs 79.1 [10.1] mm Hg), or heart rate (75.0 [7.2] vs 75.9 [9.9] bpm) were found between baseline and posttreatment values. No significant changes were observed in serum alanine aminotransferase, aspartate aminotransferase, or creatine kinase activity in any of the patients (**Table II**).

Atorvastatin was well tolerated. None of the patients required withdrawal of medication due to an adverse event. Moderate dyspepsia was seen in 1 patient.

DISCUSSION

Insulin resistance syndrome has been associated with several complications related to CVD, some of which could be life threatening.[20] Important CVD risk factors (eg, DM, hypertension, hyperlipidemia) might result in endothelial dysfunction, vascular inflammation, and prothrombotic events that might lead to atherosclerosis and its complications, such as acute coronary syndromes, sudden cardiac death, or congestive heart failure. Insulin resistance is at the center of these events.[1,13] The presence and the treatment of insulin resistance have been investigated intensively, especially in patients with type 2 DM. The Coronary Artery Risk Development in Young Adults (CARDIA) study[23] examined insulin and lipids in black and white young adults. The investigators in the epidemiologic CARDIA study[23] reported that plasma insulin levels were positively

Table II. Clinical and laboratory findings before (baseline) and after 12 weeks of treatment with atorvastatin 10 mg/d in patients with hyperlipidemia and insulin resistance (N = 15). Values are mean (SD).

Characteristic	Baseline	12 Weeks	*P*
SBP, mm Hg	124.1 (12.7)	128.3 (12.4)	0.267
DBP, mm Hg	78.7 (9.4)	79.1 (10.1)	0.821
HR, bpm	75.0 (7.2)	75.9 (9.9)	0.798
ALT, IU/dL	22.4 (9.5)	21.7 (6.1)	0.848
AST, IU/dL	24.9 (15.2)	23.5 (9.9)	0.737
CK, IU/dL	113.2 (59.4)	101.5 (42.7)	0.515

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase.

correlated with blood pressure and plasma levels of TG, TC, and LDL-C, and negatively correlated with plasma levels of HDL-C and apo A1 in both racial groups, a result independent of age, sex, and BMI. A number of methods (eg, oral glucose tolerance test, FPG, FPI, euglycemic clamp, glycosylated hemoglobin [HbA_{1c}], HOMA index) have been used to determine insulin resistance.[17,18,21] Although the euglycemic clamp is the most sensitive technique, its use is limited because it is complex and time-consuming.[18] The HOMA index is being used with increasing frequency in clinical studies[17,18,25] and has been shown to be a reliable, rapid method of determining insulin resistance. We used the HOMA index to measure insulin resistance because its results have been shown to be reliable, rapid, and scientifically accepted.[18,21,23]

In the 1994 Scandinavian Simvastatin Survival Study (4S),[28] a distinct decrease in the total mortality rate was found in 4444 patients with stable coronary artery disease and elevated TC and LDL-C levels who were treated with simvastatin. This finding promoted statin use and the onset of secondary and primary prevention studies.[25–28] Statin therapy has been found to result in mild regression of fixed atherosclerotic lesions on angiography, and statins have also been shown to have pleiotropic nonlipid effects in and around the atherosclerotic lesions.[29] Beneficial effects were found to be independent of cholesterol levels.[29] Statins have been associated with increased endothelial nitric oxide synthase levels and improved endothelial function,[30] and diminished inflammatory activity.[26,27] Statins also have been found to affect coagulation and thrombocytic functions (eg, by inhibiting thrombocytic aggregation and adhesion and by decreasing fibrinogen and plasminogen activator inhibitor 1 levels).[31]

Results from studies of the effects of statins on insulin resistance are conflicting. Various studies have found an increase, no change, or a decrease in insulin resistance.[24,30–37] Some studies[24,32,33,36] of statins have assessed efficacy in diabetic, hyperlipidemic patients, and most have used lovastatin, simvastatin, and/or pravastatin. In a randomized, single-blind study in 195 patients with type

2 DM, Paolisso et al[24] investigated the effects of statin therapy on insulin resistance using the HOMA index. Patients were randomly assigned to receive simvastatin 10 mg/d, atorvastatin 5 mg/d, or placebo for 8 weeks. Statin treatment was found to be effective in controlling dyslipidemia in these patients, and insulin resistance was decreased significantly ($P < 0.05$). In a double-blind, placebo-controlled, parallel-group study (atorvastatin 10 mg/d vs placebo) in 40 hyperlipidemic patients with type 2 DM, Tanaka et al[32] measured fasting levels of HbA_{1c} and fructosamine as indices of glycemic control. They reported that atorvastatin was well tolerated and associated with significantly decreased LDL-C, but no significant effects on glycemic control were found. Our study was different from the study by Tanaka et al[32] in that our study population was normoglycemic. The duration of treatment and the insulin resistance identification method in our study were similar to those of Paolisso et al,[24] and the atorvastatin dose used was similar to that of Tanaka et al.[32] Furthermore, like Tanaka et al,[32] we did not observe any effects on current insulin resistance with atorvastatin use. Similar conflicting results were also found in other statin studies.[33–36]

In a 9-week, randomized, double-blind, crossover study in 12 elderly patients with type 2 DM, Paolisso et al[14] compared the effects of simvastatin 30 mg/d with those of placebo. Using the euglycemic clamp method to investigate insulin sensitivity, the investigators found that simvastatin was associated with improved lipid and glucose metabolism and decreased insulin resistance significantly. Sweany et al[33] compared the lipid-altering effects and tolerability of simvastatin with those of gemfibrozil in 168 hyperlipidemic patients with type 2 DM in a 24-week, double-blind, randomized, multicenter trial. Patients were randomly assigned to receive simvastatin 10 mg QD (titrated up to 40 mg/d to achieve an LDL-C level <3.4 mmol/L) or gemfibrozil 600 mg BID. They found no significant differences between baseline and posttreatment FPG or HbA_{1c} levels between the 2 treatment groups. In a randomized, double-blind, placebo-controlled, crossover trial in 120 hyperlipidemic patients, Jula et al[34] investigated the effects of simvastatin 20 mg/d alone or in combination with a modified diet on lipid parameters and FPG. They reported improvement in lipid parameters (all, $P < 0.001$) but an increase in insulin resistance ($P = 0.005$) after 12 weeks of therapy. In a study in 18 patients with primary hyperlipidemia randomly assigned to receive simvastatin 20 mg/d or placebo for 8 weeks, Altunbas et al[35] investigated insulin sensitivity using the euglycemic clamp method. The investigators found that simvastatin treatment was not associated with any effects on short-term insulin sensitivity. Similar contradictory results have been observed in pravastatin studies. In a 14-week, prospective, open-label study in 23 patients with DM and hyperlipidemia who did not achieve the target lipid levels with low-dose (20 mg/d) pravastatin alone, Gardner et al[36] studied the effects of the addition of niacin 1.5 g/d to a regimen containing pravastatin 20 mg/d on insulin sensitivity (FPG and fructosamine levels). The investigators found no significant differences in insulin sensitivity when niacin was added to pravastatin treatment. In another study, Sheu et al[37] treated hyperlipidemic

patients with pravastatin 10 to 20 mg/d for 12 weeks and reported significant improvement in the LDL-C level but no significant improvement or even worsening of hyperglycemia, insulin resistance, impairment of glucose tolerance, and hyperinsulinemia.

Paolisso et al[24] hypothesized that the positive effects of statins on insulin resistance might be associated with decreased plasma TG levels in patients with type 2 DM, noted that elevated TG levels were associated with impaired oxidative and nonoxidative insulin-mediated glucose metabolism, and noted that reducing TG levels might be inversely correlated with glucose metabolism. Although this hypothesis seems reasonable, improvement in insulin resistance was not found in other studies of statins[33–36] or in our study, in which TG levels were markedly reduced.

Another possible hypothesis is that statins reduce mevalonate levels by inhibiting hydroxymethylglutaryl coenzyme A reductase activity. Mevalonate metabolites are effective in insulin and insulin-like growth factor I (IGF-I) signaling pathways.[38,39] The response to IGF-I and insulin in signaling pathways is reduced when vascular smooth muscle cell cultures are exposed to lovastatin.[39] In 1 study,[39] human fibroblasts treated with the antihypercholesterolemic drug, lovastatin, displayed a diminished signaling response to epidermal growth factor, insulin, and IGF-I. Supplementing the culture medium with mevalonic acid restored the signaling response. In addition, lovastatin has been found to inhibit insulin receptor/IRS-1/P-I-3 complex formation.[40] All of these effects have been eliminated with mevalonate use.[39]

It has been hypothesized that phosphatidylinositol kinase 3 inhibitors have been associated with reduced insulin-mediated glucose transport.[41] Lovastatin has been associated with a reduction in phosphatidylinositol kinase 3 levels by reducing mevalonate levels.[42] Theoretically, statins could reduce insulin-mediated glucose uptake by improving postreceptor insulin signaling, thereby reducing insulin sensitivity. When we consider this hypothesis, negative results would be expected from the studies of statins and insulin resistance because of reducing insulin-mediated glucose uptake. However, the results of most clinical studies[32,33,35,36] of statins have been neutral, and some[14–24] have had positive results; insulin resistance was not reduced with atorvastatin treatment in our study. Similar studies[14,24,33–37] have had mean treatment periods of 4 to 24 weeks. The treatment period in our study was 12 weeks. Because the patients in our study had no CVD risk factors other than insulin resistance, we found it appropriate to administer atorvastatin at a dose of 10 mg/d. We noted that previous studies also used statins at recommended doses.[14,24,33–37]

In this study, treatment with atorvastatin 10 mg/d was not associated with any significant changes in insulin resistance. However, a possible positive or negative effect of atorvastatin might have been missed due to the small sample size or the dose used. A larger study using a higher dose and a control group, together with a longer treatment period, are needed.

CONCLUSION

This short-term pilot study in patients with hyperlipidemia and insulin resistance suggested that 12-week atorvastatin treatment was effective in controlling hyperlipidemia but did not decrease the severity of insulin resistance.

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